Keynote session speech

Centrioles and Cilia in Health and Brain Disease

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Abstract

The centriole is an essential component of the centrosome, which is required for the formation of the mitotic spindle, cilia, and flagella. Centriole duplication involves the growth of a procentriole (daughter centriole) from an existing centriole (mother centriole). During the past years, my laboratory has reported several key proteins, including CPAP (Nat Cell Biol 2009, Cell Rep 2016, J Cell Sci 2020, Front Cell Dev Biol 2022), STIL (EMBO J 2011), CEP135 (EMBO J 2013), CEP120 (J Cell Biol 2013, Sci Rep 2019, Genes & Development 2021), RTTN (Nat Commun 2017), and Myosin-Va (Nat Cell Biol 2019) that participate in centriole duplication and cilia formation. Primary microcephaly (MCPH) is a neurodevelopmental disorder characterized by small brain size with mild to severe intellectual disability, while Joubert syndrome is a hereditary autosomal-recessive ciliopathy, which exhibitscerebellum-brain stem malformation. Interestingly, mutations in many centriolar protein-encoding genes were reported to cause MCPH and Joubert syndrome,but their underlining mechanisms remain incomplete understood. To study the physiological roles of centriolar proteins in brain development and their pathological linkage with neurodevelopmental disorders, we have generated both microcephaly Cpapgene conditional knockout mice and Cpap-E1241Vknockin mice that phenocopy human microcephaly patients. We also used human iPS-derived brain organoidscarrying CPAP-E1235V disease-associated mutant protein and in vivo cerebellar electroporation to study neuronal cell proliferation and differentiation in MCPH and Joubert syndrome. The results from these promising experimental models for brain development and phenotypic features ofprimary microcephaly and Joubert syndromein humans will be discussed.and the mechanistic insight learned from our studies will be presented.

Selected recent publications:

1. Lin YN, Wu CT, Lin YC, Hsu WB, Tang CJC, Chang CW, Tang TK (2013) CEP120 interacts with CPAP and positively regulates centriole elongation. J. Cell Biol.202, 211-219.

2. Chen HY, Wu CT, Tang CJC, Lin YN, Wang WJ, Tang TK (2017) Human microcephaly protein RTTN interacts with STIL and is required to build full-length centrioles. Nat. Commun. 2017, 8:247.

3. Wu CT, Chen HY, Tang TK (2018) Myosin-Va is required for preciliary vesicle transportation to the mother centriole during ciliogenesis. Nat. Cell Biol. 20, 175–185.

4. Chang CH, Chen TY, Lu IL, Li RB, Tsai JJ, Lin PY, Tang TK (2021) CEP120-mediated KIAA0753 recruitmentonto centrioles is required for timelyneuronal differentiation and germinal zoneexit in the developing cerebellum. Genes & Development. 35:1445–1460.

5. An HL, Kuo HC, Tang TK (2022) Modeling human primary microcephaly with hiPSC-derived brain organoids carryingCPAP-E1235V disease-associated mutant protein. Front Cell Dev Biol. 10:830432.